DEC - 2 2011 K110786

510(k) SUMMARY: eSensor® Warfarin Sensitivity Saliva Test on XT-8 System

Preparation Date: October 24, 2011

Submitted By:

Clinical Micro Sensor dba GenMark
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Contacts:

John Riolo, Vice President - Quality & Regulatory Affairs (Official Correspondent)

Proprietary Names and Classifications:

For the assay:
eSensor® Warfarin Sensitivity Saliva Test (Kit)

Regulation: 21CFR 864.7280
Panel: Hematology (81)
Classification: Class II
Product Codes: CYTOCHROME P450 2C9 (CYP450 2C9) DRUG METABOLIZING ENZYME GENOTYPING SYSTEM (ODW) and VITAMIN K EPOXIDE REDUCTASE COMPLEX SUBUNIT ONE (VKORC1) GENOTYPING SYSTEM (ODV)

For the instrument:
eSensor® XT-8 Instrument (System)
Regulation: 21CFR 862.2570
Panel: Clinical Chemistry (75)
Classification: Class II
Product Code: NSU - Instrument for Clinical Multiplex Test Systems

Common name:
Warfarin Sensitivity Saliva
CYP450 2C9 *2 and CYP450 2C9 *3 alleles and VKORC1 Genotyping

Intended use:
The eSensor® Warfarin Sensitivity Saliva Test is an *in vitro* diagnostic test for the detection and genotyping of the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the Vitamin K epoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A) from genomic DNA of human saliva samples collected using the Oragene® Dx Device, as an aid in the identification of patients at risk for increased warfarin sensitivity.

Special conditions for use statement(s):
The eSensor® Warfarin Sensitivity Saliva Test can provide information to the physician and lab director on the genotype and allele designation of the three (3) polymorphisms stated in the intended use. However, determination of the therapeutic strategy and treatment dose for Warfarin will depend on multiple additional factors and are beyond the scope of the eSensor® Warfarin Sensitivity

Saliva Test Report and Package Insert.

The eSensor® Warfarin Saliva Sensitivity Test is for *in vitro* diagnostic use within a licensed laboratory, as defined by the Clinical Laboratory Improvement Amendments (CLIA) of 1988.

Predicate devices:
K073720 eSensor Warfarin Sensitivity Test eSensor XT-8 System

Device Description:

The eSensor® Warfarin Sensitivity Saliva Test is a multiplex microarray-based genotyping test system. It is based on the principles of competitive DNA hybridization using a sandwich assay format, wherein a single-stranded target binds concurrently to sequence-specific solution-phase signal probe and solid-phase electrode-bound capture probe. The test employs polymerase chain reaction amplification, exonuclease digestion and hybridization of target DNA. In the process, the double stranded PCR amplicons are digested with exonuclease to generate single stranded DNA suitable for hybridization. Hybridization occurs in the eSensor® XT-8 Cartridge (described below) where the single-stranded target DNA is mixed with a hybridization solution containing labeled signal probes.

During hybridization, the target DNA binds to a complementary, single-stranded capture probe immobilized on the working electrode surface. Single-stranded signal probes (labeled with electrochemically active ferrocenes) bind to the target adjacent to the capture probe. When inserted into the eSensor® XT-8 instrument (described below), simultaneous hybridization of target to signal probes and capture probe is detected by alternating current voltammetry (ACV). Each pair of working electrodes on the array contains a different capture probe, and sequential analysis of each electrode allows genotyping of multiple mutations or polymorphisms.

The Assay Cartridge (eSensor® XT-8 Cartridge)

The eSensor® XT-8 cartridge device consists of a printed circuit board (PCB) with a multi-layer laminate and a plastic cover that forms a hybridization chamber. The chamber has a volume of approximately 140 µl. The cartridge consists of a diaphragm pump and check valves (microfluidic components) that circulate the hybridization solution in the hybridization chamber when inserted into the eSensor® XT-8 instrument. The PCB chip consists of an array of 72 gold-plated working electrodes, a silver/silver chloride reference electrode, and two gold-plated auxiliary electrodes. Each working electrode has a connector contact pad on the opposite side of the chip for electrical connection to the eSensor® XT-8 instrument. Each electrode is modified with a multicomponent, self-assembled monolayer that includes presynthesized oligonucleotide capture probes specific for each polymorphic site on the test panel and insulator molecules. The cartridge also contains an electrically erasable programmable read-only memory component (EEPROM) that stores information related to the cartridge (e.g., assay identifier, cartridge lot number, and expiration date).

The eSensor® XT-8 Instrument (Same as cleared under k073720)

The eSensor® XT-8 is a clinical multiplex instrument that has a modular design consisting of a base module and one, two, or three cartridge-processing towers containing 8, 16, or 24 cartridge slots, respectively. The cartridge slots operate independently of each other. Any number of cartridges can be loaded at one time, and the remaining slots are available for use while the instrument is running.

The base module controls each processing tower, provides power, and stores and analyzes data. The base module includes the user interface, and a 15-in. portrait-orientation display and touch panel. The instrument is designed to be operated solely with the touch screen interface. Entering patient accession numbers and reagent lot codes can be performed by the bar code scanner, the touch screen, or uploading a text file from a USB memory stick.

Each processing tower consists of eight cartridge modules, each containing a cartridge connector, a precision-controlled heater, an air pump, and electronics. The air pumps drive the diaphragm pump and valve system in the cartridge, eliminating fluid contact between the instrument and the cartridge. The pneumatic pumping enables recirculation of the hybridization solution allowing the target DNA and the signal probes to hybridize with the complementary capture probes on the electrodes. The diaphragm pump in the cartridge is connected to a pneumatic source from the eSensor XT-8 instrument and provides unidirectional pumping of the hybridization mixture through the microfluidic channel during hybridization. Using microfluidic technology to circulate the hybridization solution minimizes the unstirred boundary layer at the electrode surface and continuously replenishes the volume above the electrode that has been depleted of complementary targets and signal probes.

The XT-8 instrument provides electrochemical detection of bound signal probes by ACV and subsequent data analysis and test report generating functions. All hybridization, ACV scanning and analysis parameters are defined by a scanning protocol loaded into the XT-8 Software, and then specified for use by the EEPROM on each cartridge.

The Assay Kit

The Warfarin Sensitivity Saliva Test consists of the test cartridge and the following components: 1) PCR REAGENTS consisting of: PCR Mix [PCR buffer containing primers and dNTP mixture (dCTP, dGTP, dATP, and dUTP)], $MgCl_2$, thermostable DNA polymerase (Taq Polymerase); and 2 GENOTYPING REAGENTS consisting of: lambda exonuclease, signal probes and hybridization buffer ingredients (Buffer-1 and Buffer-2).

Comparison to technological features of the predicate devices:

The following is a comparison of the GenMark Diagnostics eSensor® Warfarin Sensitivity Saliva Test on the XT-8 System to the predicate: Warfarin Sensitivity Test (**K073720)**

Characteristic	eSensor® Warfarin Sensitivity Test **(Predicate: K073720)**	eSensor® Warfarin Sensitivity Saliva Test
Test type	Qualitative genetic test for single nucleotide polymorphism detection	Same as predicate
Sample Type	Genomic DNA obtained from a human whole blood sample	Genomic DNA obtained from a human saliva sample
Target of detection	Single-nucleotide polymorphism	Same as predicate
DNA extraction	Performed off-line	Same as predicate
Genes	CYP450 2C9 gene *2 allele CYP450 2C9 gene *3 allele VKORC1 gene -1639G>A polymorphism	Same as predicate
Number of Loci genotyped	3	Same as predicate
Genotyping reaction location	Test cartridge	Same as predicate
Genotyping principle	Sandwich hybridization test	Same as predicate
Instrument operating system	eSensor® Instrument Model XT-8 Random access compatible with multiple simultaneous test types.	Same as predicate
Assay results	Assay signal results are interpreted by a software program and are assigned a result that is presented to the end-user in a report format	Same as predicate

Performance Characteristics:

Method Comparison

In a method comparison study, a total of 316 gDNA samples extracted from saliva specimen with A260-280 ratios of 1.2-2.1 were genotyped using the eSensor® Warfarin Sensitivity Saliva Test and DNA sequencing.

eSensor® Warfarin Sensitivity Saliva Test Method Comparison Before Retest			
DNA Sequencing Result	2C9 wt/wt	2C9 wt/*2	2C9*2/*2
Correct Calls	234	69	9
No-Calls	3	0	0
Miscalls[1]	0	1	0
%Agreement	98.7%	98.6%	100.0%
95% LCB	96.8%	93.4%	71.7%
DNA Sequencing Result	2C9 wt/wt	2C9 wt/*3	2C9 *3/*3
Correct Calls	274	34	3
No-Calls	3	0	0
Miscalls[2]	2	0	0
%Agreement	98.2%	100.0%	100.0%
95% LCB	96.3%	91.6%	36.8%
DNA Sequencing Result	VKORC1 G/G	VKORC1 G/A	VKORC1 A/A
Correct Calls	120	131	62
No-Calls	2	1	0
Miscalls	0	0	0
%Agreement	98.4%	99.2%	100.0%
95% LCB	94.9%	96.5%	95.3%

[1] Miscall was due to a 2C9 *2 interfering mutation at 429C>T.

[2] The other two miscalls were due to 2C9 *3 low signal caused by sample extractions.

eSensor® Warfarin Sensitivity Saliva Test Method Comparison After Retest			
DNA Sequencing Result	2C9 wt/wt	2C9 wt/*2	2C9*2/*2
Correct Calls	237	69	9
No-Calls	0	0	0
Miscalls[1]	0	1	0
%Agreement	100.0%	98.6%	100.0%
95% LCB	98.7%	93.4%	71.7%
DNA Sequencing Result	2C9 wt/wt	2C9 wt/*3	2C9 *3/*3
Correct Calls	277	34	3
No-Calls	0	0	0
Miscalls[2]	2	0	0
%Agreement	99.3%	100.0%	100.0%
95% LCB	97.8%	91.6%	36.8%
DNA Sequencing Result	VKORC1 G/G	VKORC1 G/A	VKORC1 A/A
Correct Calls	122	132	62
No-Calls	0	0	0
Miscalls	0	0	0
%Agreement	100.0%	100.0%	100.0%
95% LCB	97.6%	97.8%	95.3%

[1] Miscall was due to a 2C9 *2 interfering mutation at 429C>T.

[2] The other two miscalls were due to 2C9 *3 low signal caused by sample extractions.

Interference Substances

Effect of Endogenous Interfering Substances: Interfering substances including salivary α-amylase, hemoglobin, immunoglobulin A (IgA) and total protein were spiked into saliva samples at the highest amounts found in literature. 10 donors provided five saliva samples each which were each spiked with one of the four interfering substances. A control sample was included. Three extractions were performed on each sample. There was 100% agreement between the eSensor® Warfarin Sensitivity Saliva Test results and bidirectional DNA sequencing for all test substances in first pass, demonstrating no effect of any interfering substances on genotyping.

Substance	Concentration	Samples Tested	Correct Calls	Incorrect Calls	No-Calls	% Agreement
Control	NA	30	30	0	0	100%
Amylase	260 ± 45 U/mL	30	30	0	0	100%
Hemoglobin	20 mg/mL	30	30	0	0	100%
IgA	188 ± 80 mg/L	30	30	0	0	100%
Total Protein	1.46 ± 0.4 mg/mL	30	30	0	0	100%

Effect of Exogenous Interfering Substances: Potentially interfering exogenous substances (eating, drinking, chewing gum, using mouthwash and smoking) introduced into saliva samples through various activities were tested. Each activity group was composed of five donors who each provided samples for baseline, immediate and 30 minutes. Three samples per donor were tested. There was 100% agreement between the eSensor® Warfarin Sensitivity Saliva Test results and bidirectional DNA sequencing for all activities tested in first pass, demonstrating no effect of any interfering substances on genotyping.

Activity	Time-point	Samples Tested	Correct Calls	Incorrect Calls	No-Calls	% Agreement
Eating	Baseline	15	15	0	0	100%
	Immediate	15	15	0	0	100%
	30 minutes	15	15	0	0	100%
Drinking	Baseline	15	15	0	0	100%
	Immediate	15	15	0	0	100%
	30 minutes	15	15	0	0	100%
Chewing Gum	Baseline	15	15	0	0	100%
	Immediate	15	15	0	0	100%
	30 minutes	15	15	0	0	100%
Mouthwash	Baseline	15	15	0	0	100%
	Immediate	15	15	0	0	100%
	30 minutes	15	15	0	0	100%
Smoking	Baseline	15	15	0	0	100%
	Immediate	15	15	0	0	100%
	30 minutes	15	15	0	0	100%

Conclusion:
The above clinical test results support the safety and effectiveness of the eSensor® Warfarin Sensitivity Saliva Test on the eSensor® XT-8 System, and demonstrate substantial equivalence to the predicate device.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

10903 New Hampshire Avenue
Silver Spring, MD 20993

GenMark Diagnostics, Inc.
c/o John Riolo
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DEC - 2 2011

Re: k110786
Trade Name: eSensor Warfarin Sensitivity Saliva Test
Regulation Number: 21 CFR §862.3360
Regulation Name: Drug Metabolizing Enzyme Genotyping System
Regulatory Class: Class II
Product Codes: ODW, ODV, NSU
Dated: October 24, 2011
Received: October 27, 2011

Dear Mr. Riolo:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (301) 796-5760. For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance...

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-5680 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm

Sincerely yours,

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use Form

510(k) Number (if known): K110786

Device Name: eSensor® Warfarin Sensitivity Saliva Test

Indications for Use:

The eSensor® Warfarin Sensitivity Saliva Test is an *in vitro* diagnostic for the detection and genotyping of the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the Vitamin K epoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A) from genomic DNA extracted from human saliva samples collected using the the Oragene® Dx Device, as an aid in the identification of patients at risk for increased warfarin sensitivity.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

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